AVAC

AIDS Vaccine Advocacy Coalition

Advocacy to accelerate ethical research & global delivery of AIDS vaccines

April 29, 2005

Via E-Mail FDADockets@oc.fda.gov
And hardcopy followup by U.S. Mail

Division of Dockets Management (HFA-305)
Food and Drug Administration (FDA)
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: Comments on FDA's Draft Guidance for Industry: Considerations for Plasmid DNA Vaccines for Infectious Disease Indications (DNA Vaccine Guidance) - 70 Fed. Reg. 8378, February 18, 2005 – **Docket No. 2005D-0047**

To the Food and Drug Administration:

The AIDS Vaccine Advocacy Coalition (AVAC) appreciates this opportunity to comment on the FDA's draft DNA Vaccine Guidance.[1] AVAC is a volunteer and nonprofit public interest organization dedicated to ethical research and accelerating global delivery of vaccines to fight the AIDS pandemic. To further that mission, AVAC supports the FDA's active engagement bringing clarity, direction and assistance to the complicated, multicentered AIDS vaccine research agenda and making that research more efficient and productive. The draft DNA Vaccine Guidance is an example of the FDA's contribution.

We encourage the Agency to develop guidance on other difficult questions affecting reviews of vaccine research or to implement AIDS vaccine product discovery and stimulation initiatives - for example through the Critical Path program - to combat this global health emergency. We hope those efforts will be a priority. They are necessary to address what is probably the most difficult health science question today.[2] Much work remains to be done to identify correlates of protection and the delivery of safe, efficacious vaccines. Our specific comments on the DNA Vaccine Guidance are as follows:

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[1] http://www.fda.gov/cber/gdlns/plasdnavac.pdf .

[2] "This is one of the most difficult problems in science today," said Dr. Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases. G-8 nations back global research for AIDS vaccine, Seattle-Post Intelligencer, June 11, 2004 http://www.seattlepi.com/health/177369_hiv11.html

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ASSAYS FOR IMMUNOLOGICAL POTENCY – DNA VACCINE GUIDANCE,IV.B.,P. 6

The DNA Vaccine Guidance states:

> We recommend that you develop assays to assess immunological potency in animal models. This could include the evaluation of antigen-specific antibody titers, seroconversion rates, activation of cytokine secreting cells, and/or measures of cell-mediated immune responses. Optimally, these studies are designed to collect information regarding the duration of the immune response.

The question of which assays of immunological potency provide direction for further testing of candidate AIDS vaccines is one of the vexing problems in AIDS vaccine research. The examples cited in the DNA Vaccine Guidance must figure prominently in all preclinical and clinical trial stages. But there is as yet no confirmation which specific assays or combinations truly measure protective correlates or markers, predictive in the short term, for durability, resistant to escape mechanisms, applicable to multiple and variable virus challenge or applicable to humans. Just as a single example from the literature, footnoted here, (and there are others), the most logically expected assay evaluations may lack predictive power to identify successful vaccine candidates in animals.[3] It may be important to identify more than one correlate.

Because the verification of appropriate assays is not sufficiently developed, AVAC recommends using more flexible language in this section of the guidance. The guidance could state, instead:

> Currently, the most significant assays include the evaluation of antigen-specific antibody titers, seroconversion rates, activation of cytokine secreting cells, and/or measures of cell-mediated immune responses. However, other measures of potency, singly or in combination, may turn out to be more predictive. Optimally, these studies are designed to collect information regarding the duration of the immune response or capable of evaluating various immune responses, perhaps, when appropriate, in settings of multiple and variable virus challenge or resistant to escape mechanisms.

AUTOIMMUNITY – DNA GUIDANCE, IV.C. AND E., PP. 6,7.

The DNA Vaccine Guidance states:

> Published preclinical studies indicate that DNA vaccination can activate autoreactive B cells to secrete IgG anti-DNA autoantibodies (See Section VI, References). However, the magnitude and duration of this response appears to be insufficient to cause disease in

[3] Singh DK, Liu Z, Sheffer D, Mackay GA, Smith M, Dhillon S, Hegde R, Jia F, Adany I, Narayan O. (2005) A noninfectious simian/human immunodeficiency virus DNA vaccine that protects macaques against AIDS**.** J Virol. 79(**6**):3419-28. (The abstract states: "These results established that noninfectious DNA of pathogenic SHIV could be used as a vaccine to prevent AIDS, even though the immunological assays used did not predict the manner in which the challenge virus would replicate in the vaccinated animals.")

> normal animals or accelerate disease in autoimmune-prone mice. These preclinical studies helped to establish that systemic autoimmunity is unlikely to result from DNA vaccination. Similarly, the absence of an immune response against cells expressing the vaccine-encoded antigen (including muscle cells and dendritic cells) suggests that an autoimmune response directed against tissues in which such cells reside is unlikely. Based on these findings, we will no longer expect that you perform preclinical studies to specifically assess whether vaccination causes autoimmune disease. …
>
> For DNA vaccines that co-express cytokine genes, you should consider specific preclinical studies in animal species responsive to the encoded human cytokine or models using the analogous animal genes to assess whether modulation of the cellular or humoral components of the immune system might result in unintended adverse consequences, such as generalized immunosuppression, chronic inflammation, autoimmunity or other immunopathology.

The two subsections of the DNA Vaccine Guidance may not be sufficiently clear in providing direction – on the one hand no longer expecting preclinical assessment in DNA vaccination for autoimmune disease and on the other laying out circumstances where specific preclinical studies must be considered for DNA vaccines that co-express cytokine genes. For any given cytokine, it may be important to evaluate the need for other studies. If there is a system where the data are relatively well developed, perhaps the need for other studies may be reduced.

AVAC also holds the view that "good guidance" practice/procedure should avoid using guidelines as the place to record far reaching scientific conclusions determinative of complex safety issues. The DNA Vaccine Guidance cannot be sufficiently nimble to lay out all of the numerous studies and support that may affirm or contradict the conclusion that "systemic autoimmunity [or against tissues] is unlikely to result from DNA vaccination." These broad conclusory statements may have a chilling effect on promoting studies or trial designs that could detect serious *unexpected* adverse events. Typically, safety conclusions are not stated with this level of authority to affirm "negative causation." When biologically plausible mechanisms are under review, the typical form may be to state instead: "There is not sufficient evidence to show that DNA vaccination results in autoimmunity." In any case, guidance is not the best forum to state these conclusions.

It is useful to provide direction regarding the preclinical toxicity data set necessary for product and clinical trial review. Based on current scientific consensus, it may be appropriate not to expect preclinical autoimmunity studies for DNA vaccines. We request that FDA determine the usefulness of such studies after further exploration of the best consensus and clarify requirements in the DNA Vaccine Guidance. In addition, FDA might determine in this or future guidance which directions for study are not specifically related to the vector (e.g. DNA, live virus, recombinant protein, heterologous vector), classify those that may not differ from those with other vaccine modalities and, thereby, expand its efforts to assist researchers in planning and design.

Thank you for consideration of these requests. Please contact either Mitchell Warren, Executive Director (Tel: 212/367-1084; email: mitchell@avac.org) or Robert Reinhard, Board Member (Tel: 415/268-7469; email: robert@avac.org) for questions or response you may have.

Very Truly Yours,

Mitchell Warren, Executive Director

Robert Reinhard, Board Member

CC: Joseph L. Okrasinski, CBER (joseph.okrasinski@fda.hhs.gov)